660.5
S99S
THE JOHN CRERAR
LIBRARY

SYNTHETIC ORGANIC CHEMICALS

PUBLISHED BY THE

Eastman Kodak Company, Rochester, N. Y.

VOL. XII OCTOBER, 1940 No. 4

Synthesis of Macrocyclic Compounds

*Part II—High-Dilution Method**

G. F. FRAME

Research Laboratories—Eastman Kodak Company

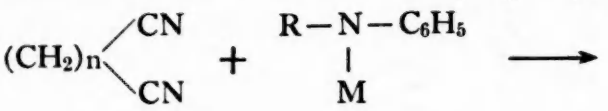
In the synthesis, by intramolecular ring closure, of cyclic compounds having more than 6 members, the small yields result from the occurrence of side reactions of two main types:

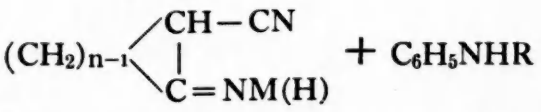
1. Polymerization—the coupling of the end of one reacting molecule with the end of another molecule instead of with itself, to form, after many repetitions, a polymer.
2. Monomolecular side reactions—as an example, the formation, from a hydroxycarboxylic acid, of an unsaturated acid instead of a lactone—

$$HO(CH_2)_nCOOH \longrightarrow CH_2=CH(CH_2)_{n-2}COOH$$

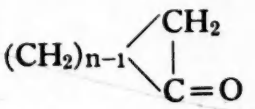
Ziegler was successful in synthesizing several different types of polymembered ring compounds by employing reactions known to be irreversible and free from side reactions, and by the use of very dilute solutions in order to suppress polymerization. The principle of minimizing polymerization by carrying out the reaction at high dilution was first suggested by Ruggli, in 1912; but its value as a means of synthesizing macrocyclic compounds was completely overlooked until 1933.

It was at this time that Ziegler began his series of brilliant researches. His earliest, and probably his most successful, investigation dealt with the action of an alkali-metal alkyl anilide on dinitriles of dibasic acids, which may be represented by the following general equation wherein M indicates one of the alkali metals and R an alkyl group—

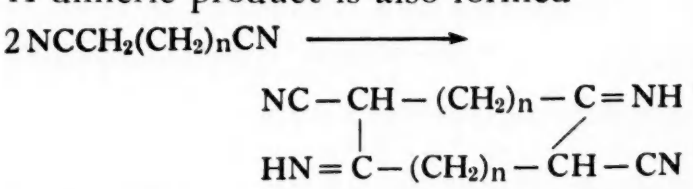




The resulting cyanoketimides may then be readily hydrolyzed to the corresponding cyclic ketones—



A dimeric product is also formed—



This cyclic dinitrile is easily hydrolyzed to the diketone.

The series of monomeric ketones from C_5 to C_{29}, with the exception of C_{27}, has

*The first of the two general procedures for the synthesis of macrocyclic compounds, the depolymerization or radical-interchange method, was discussed in *Synthetic Org. Chem.*, *12*, No. 3 (1940).

been prepared by this method; as also has been ketone C_{33}. The yields varied over a wide range. The C_5 to C_8 compounds, inclusive, were formed in yields of better than 90%, while yields of less than 1% of the C_9, C_{10}, and C_{11} ketones were obtained. An abrupt increase in the yield occurred when C_{14} and C_{15} were reached and from this point upward varied from 60-80%. In this last portion of the series, C_{15} to C_{29}, a periodicity in yields was apparent, the compounds that had an even number of carbon atoms being formed in about 10% larger amounts than their odd-numbered homologues. In the cyclization of dinitriles having 10, 11, or 12 carbon atoms, dimeric compounds are the principal products, being formed in yields of 60-70%; these are easily hydrolyzed to the corresponding symmetrical

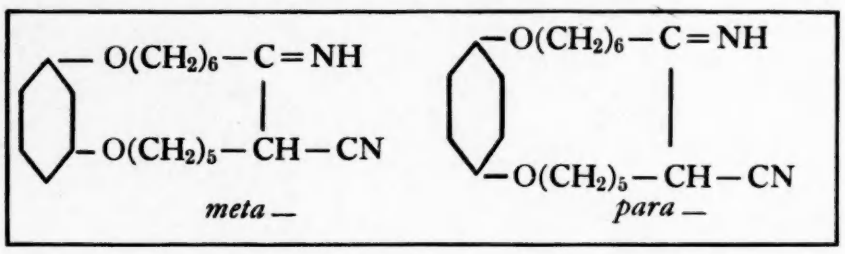


FIGURE 1—*Meta and para ring closure*

diketones that have 18, 20, and 22 carbon atoms. The yields of dimeric ring compounds from the C_{13} and C_{14} dinitriles are also high.

One of the most interesting of Ziegler's syntheses was that of *r*-muskone. Ruzicka had proved this compound to be β-methylcyclopentadecanone, but he was not successful in its preparation. His method of synthesis of large rings by the dry distillation of certain salts of dicarboxylic acids fails when, as in this case, there is a methyl group in a position α or β to one or both carboxyl groups. Ziegler, using the high-dilution principle, obtained *r*-muskone in small yields from the dinitrile—

$$NC(CH_2)_{12}-CH(CH_3)-CH_2CN$$

Ziegler also applied the high-dilution method to the synthesis of compounds containing ethereal oxygen in the ring. By the cyclization of ω,ω′-dicyanodibutyl ether, he obtained 5-cyano-6-imidononamethylene oxide—

$$NC(CH_2)_4O(CH_2)_4CN \rightarrow O\begin{cases}(CH_2)_3-CH(CN)\\(CH_2)_4-C=NH\end{cases}$$

In the synthesis of this ether and a number of its homologues the interesting fact was disclosed that the presence of oxygen in the compound greatly increases the tendency to ring formation. In the case of this 10-membered, oxygen-containing ring compound, the yield, 5%, is more than 10 times that of the 10-membered ring compound in the polymethylene ketone series; with a 13-membered ring compound containing 2 oxygen atoms, the ratio of the yields is 70 to 12.

Ring closure in the benzene series, in the meta and para positions, was also investigated by Ziegler in the same general manner. Resorcinol [7-imino-8-cyanotridecamethylene(1,13)] ether, Figure 1, was synthesized, with a yield of 52%; and, in an analogous manner,

Reaction I

$$CH_3C_6H_4SO_2NH_2 + Br(CH_2)_6Br \xrightarrow[\text{alcoholate}]{\text{sodium}} CH_3C_6H_4SO_2NH(CH_2)_6Br$$

Reaction II

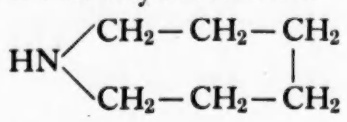
$$CH_3C_6H_4SO_2NH(CH_2)_6Br \xrightarrow[170^\circ]{\text{sodium alcoholate}}$$

$$CH_3C_6H_4SO_2-N\begin{cases}CH_2-CH_2-CH_2\\CH_2-CH_2-CH_2\end{cases} \xrightarrow{\text{hydrolysis}} HN\begin{cases}CH_2-CH_2-CH_2\\CH_2-CH_2-CH_2\end{cases}$$

FIGURE 2—*Reactions involved in the preparation of hexamethyleneimine*

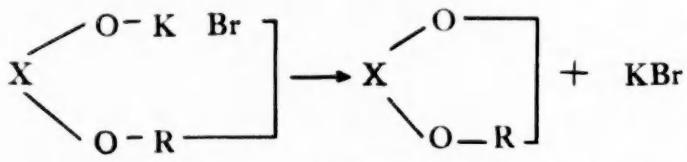
the corresponding p-ring compound was obtained, also with a 52% yield.

Another interesting application of the high-dilution method is in the preparation of hexamethyleneimine—



The reactions involved are shown as Figure 2. Reaction I is carried out at high concentration. Reaction II is run at high dilution by slowly adding equivalent amounts of dilute solutions of the first reaction product and sodium alcoholate to a large volume of benzyl alcohol maintained at 170°. A yield of 74% of toluenesulfonylhexamethyleneimine is obtained from the dilute solution, while the yield from a concentrated solution is only 25%.

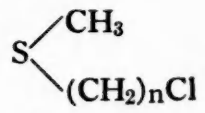
Recently Ziegler and Lüttringhaus applied the high-dilution principle to a new reaction—ring closure in phenolic ethers—according to the following equation in which X represents an aromatic residue and R an alkyl group—



This procedure has been found to be quite free from disturbing side reactions, when carried out under the proper conditions. It also has the important advantage over the dinitrile type of ring closure of utilizing more readily available starting materials.

Macrocyclic compounds have been prepared from several half-ethers of hydroquinone, resorcinol, catechol, dihydroxynaphthalene, dihydroxydiphenylmethane, and dihydroxydiphenyloxide; but attempts to cyclicize ethers of dihydroxydiphenyl have failed. The yields obtained in the catechol series varied from 40-100%; and it is interesting to note that the yield curve does not reach a minimum in the region of the 10- to 13-membered ring compounds, as is the case in the polymethylene ketone series. In regard to the other cyclic compounds investigated, it was found that, in general, the minimum length of the alkyl group (alkyl "bridge") is about $(CH_2)_7$. With a shorter "bridge" no cyclization occurs, presumably because of strain due to the close packing of the atoms that would be involved in a smaller ring. When the "bridge" length is 8 to 10 carbon atoms, yields of 20-80% are obtained. An unanticipated finding was that the yields obtained from the ring closure of several half-ethers of the dihydroxydiphenylmethane series were much higher than yields obtained from the corresponding ethers of the diphenyl oxide series; because of the "oxygen effect"—the tendency to increase ring formation—in the polymethylene series, the opposite result would be expected.

Müller recently applied the high-dilution method in the synthesis of 13-, 14-, and 15-membered cyclic sulfides by the action of alcoholic sodium sulfide on the appropriate polymethylene dibromides. A yield of 42% of the 15-membered ring sulfide was obtained.

Bennett subsequently prepared cyclic sulfides of 15, 17, and 19 members, in unstated yields, by heating compounds of the type—  to drive off CH_3Cl.

The work of Ruzicka, Carothers, Stoll, and others established the fact that the odor of macrocyclic compounds is a function mainly of ring size—the odor changing from a camphoraceous to a cedarlike and then to a musk quality as the number of ring members increases. This has been confirmed by some of the new macrocyclic compounds synthesized by the high-dilution method. For example, the 14-membered hydroquinoneoctamethylene ether and the 16-membered decamethylene ether both have a characteristic cedarwood odor; but that of the latter is somewhat softer and tends to the musk type. Even in the case of the sulfides, the odor of musk is apparent when there are 15 atoms in the ring.

Eastman Organic Chemicals as Analytical Reagents

I. REAGENTS FOR VANADIUM

8-Hydroxyquinoline-5-Sulfonic Acid

Molland, *Compt. rend.*, **210**, 144 (1940)

Very small amounts of metavanadates can be detected colorimetrically, with an accuracy of within 2%, by the use of 8-hydroxyquinoline-5-sulfonic acid. A permanent brown color that is proportional to the metavanadate concentration is formed, even in solutions containing as little as 5×10^{-5} gm. mol. per liter. In more concentrated solutions, greater accuracy is attainable. Quantitative values may be obtained by determination of the extinction coefficient of the solution.

Cupferron

Finkelschtein and Elenevich, *Zavodskaya Lab.*, 7, 665 (1938)

Cupferron can be used to determine vanadium colorimetrically in concentrations of 0.001 mg. per liter, even in the presence of up to 6 or 7 times as much chromium. The vanadium salt solution is acidified with concentrated sulfuric acid, and small amounts of potassium sulfate and hydrogen peroxide added. An aliquot portion is mixed with the cupferron solution, and gum arabic added for stabilization. Comparison with standards is made, using a nephelometer or colorimeter. The presence of Zn, Cd, Pb, Hg, Mo, Al, H_3PO_4, $B(OH)_3$, and H_3AsO_3 does not affect the determination.

p-Phenetidine

Szebellidy and Ajtai, *Mikrochemie*, **26**, 72 and 87 (1939)

Vanadium can be determined qualitatively or quantitatively by utilization of its catalytic effect on the reaction between p-phenetidine and potassium bromate. Its presence is indicated by the appearance of a violet tint a few moments after the addition of solutions of p-phenetidine, potassium bromate, and catechol; the last mentioned activates the vanadium catalyst. As little as 0.001 γ of vanadium can be detected.

For a quantitative determination, carefully measured amounts of p-phenetidine and catechol solutions are added to a 5% solution of potassium bromate. This reaction mixture is then transferred to the optical vessel of a photometer, and the time required for the galvanometer needle to reach a given scale division is recorded. The value is used to calculate the quantity of vanadium present; as little as 0.0006 γ can be determined.

Barium Diphenylamine Sulfonate

Pevtsov, *Zavodskaya Lab.*, 7, 286 (1938)

In the determination of vanadium by the Kolthoff and Sarver method, the titration is performed with ferrous sulfate, using barium diphenylamine sulfonate and diphenylamine as indicators. Interference by tungsten is avoided if a large excess of 85% H_3PO_4 is added previous to addition of the indicators.

Rochelle Salt, Mannitol, Glycerol, and Sucrose

Zolotukhin, *J. Applied Chem. (U.S.S.R.)*, **10**, 1656 (1937)

The salts of quadrivalent vanadium liberate equivalent amounts of acid with Rochelle salt, mannitol, glycerol, and cane sugar. The free acid in the salt solution is determined volumetrically.

α-Nitroso-β-Naphthol

Schemyakin and Belolson, *Compt. rend. acad. sci. U.R.S.S.*, **18**, 277 (1938)

A solution of α-nitroso-β-naphthol in either 96° alcohol or 50% acetic acid can be used for drop reactions with vanadates and molybdates. A basic solution of NH_4VO_3 gives a green color, then a green precipitate, with the alcoholic reagent; in an acid solution, a voluminous brown-red precipitate is formed; when neutral, no precipitate appears.